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SPECT (HMPAO) SUPPORT FOR ACTIVATION OF THE MEDIAL PREFRONTAL CORTICES DURING TOE GRAPHAESTHESIA[1]

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Summary.—This experiment was designed to test the construct validity of psychometric analyses that suggested a strong functional association between the accuracy for toe graphaesthesia and selective activation of neurons within the medial prefrontal regions. Single Photon Emission Computerized Tomography (SPECT) profiles were obtained for three volunteers (2 men, 1 woman) after they had been exposed to a toe graphaesthesia task or had been exposed to the control setting. The two measurements for each participant were separated by at least one week. Qualitative evaluation, using criteria employed for clinical diagnoses, of serial coronal, sagittal, and horizontal sections clearly indicated a specific increase in uptake of tracer within the rostral one-third to one-half of the medial prefrontal cortices of all three subjects during the toe graphaesthesia task compared to that during baseline conditions. The results are consistent with our neuropsychological research which indicates that toe graphaesthesia may be an accurate and useful indicator of the functional integrity of the medial surfaces of the anterior cerebral hemispheres.

The medial prefrontal and anterior cingulate cortices can be disproportionately affected during closed head injuries involving sudden acceleration or deceleration of the head and transient compression or distention of the cerebral volume. We (Persinger & Richards, 1995) have been investigating the potential utility of toe graphaesthesia from which to infer functional integrity within this region. Standardized scores for this task, in which the procedures of finger graphaesthesia (identifying numbers drawn on the skin while the patient's eyes are closed) are applied to the toes, are most strongly correlated with tasks on which performance is associated with metabolic activation within the medial prefrontal region. However, the attribution of this shared source of variance to the medial prefrontal region has been inferential.

The present study was designed to discern if there was verifiable, temporally contingent activation within the medial prefrontal cortices during toe graphaesthesia. Although SPECT (Single Photon Emission Computer Tomography) employing $^{99}Tc^{m}$-hexamethylpropylene amine oxime (HMPAO) has been considered less sensitive than PET (Positron Emission Tomography) to discern subtle changes in neurocognitive states, the level of resolu-

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tion of the former technology should be sufficient to discern activation by neuropsychological tasks which involve a relatively small, unique functional population of neurons that respond to stimulation (input) by a disproportionately increased tissue perfusion (and subsequent trapping) of HMPAO.

On the basis of the strength of the psychometric associations between tasks whose normality traditionally involves the prefrontal regions, we predicted that the HMPAO-SPECT technique would yield discriminable, qualitative results in response to the toe graphaesthesia task. Pilot studies, however ($n=2$ volunteers) had indicated that the perfusion pattern of normal brains may be associated with the auditory and visual background of the hospital environment. Even a "quiet" environment was associated with multiple, frequent auditory stimuli. These potential masking factors were considered during the design of the present study.

Method

Subjects

Two men (ages, 23 years and 24 years) and one woman (22 years) volunteered as participants; they were enrolled in a second-year clinical neuropsychology class. The participants were fully informed about the procedure, and the protocol was approved by the hospital's ethics committee. The participants reported no evidence of psychiatric histories or previous head injuries. All measurements and procedures were completed within the Department of Nuclear Medicine at the hospital.

Procedure

Each participant remained in a supine position, with the eyes and ears covered during a 10-min. period. Each participant completed this procedure twice one week apart. For two of the subjects, the first trial was the baseline while for the third participant the first trial involved the toe stimulation. During the 10-min. baseline the participant was instructed to remain quiet and to relax. There was no stimulation of the toes. During the stimulation condition, the participant was requested to identify numbers drawn upon the toes by a metal stylus according to the procedures described by Richards and Persinger (1992). At the end of the 10-min. period, a radioactive tracer was injected into an arm vein through a catheter that had been inserted before the experiment began and while the participant could see the procedure. We injected the tracer after the stimulation because (1) we wanted to ensure the neurons within the appropriate region had been stimulated sufficiently and (2) between 3% to 7% (maximum possible value) of the tracer is absorbed within 1 min. after injection.

After 30 min. the participants then reclined on a tomographic bed. Images were acquired, while the head of the participant was positioned within a holder, by a single-headed Elscint APEX SP4 tomography camera employ-

ing a low energy, high resolution collimator (FWHM 9.4 mm). There was continuous acquisition with 120 frames at 25 sec. per frame in a 64 × 64 word matrix. The magnification factor was 1. The camera window was centred on 140 kev (± 20%). Images were normalized to correct for flooding and then backprojected employing a Hamming filter supplied by the manufacturer for HMPAO-SPECT images. Attenuation was corrected by the Chang method (1978). Images were reconstructed in standard orientations around the orbitomeatal line. Data for each participant and condition were given a code for storage in computer memory.

Successive sections along the horizontal, sagittal, and coronal planes of the cerebrum were referenced against the uptake of tracer within the cerebellum for the baseline and for the stimulated conditions for each subject. Effectively each subject served as his own control. The relative uptake was displayed as a range of colors from blue (less uptake) to red (more uptake). Brain volume was partitioned qualitatively into 14 areas for each hemisphere (28 for both) which included, along the lateral surface occipital, caudal temporal, anterior temporal, superior parietal, inferior parietal, orbitofrontal, frontal, and frontal pole regions, and along the medial surface dorsal occipital, parietal, frontal or cingulate, ventral occipital, temporal or limbic, and prefrontal regions. These general regions were reliably discernable by the second author, the Director of Nuclear Medicine for the Facility, and had been routinely and reliably employed for interpretations for more than one hundred cases.

Results

During the baseline conditions all three participants showed relatively elevated uptakes of tracer within the posterior medial parietal region, posterior temporal lobes and prefrontal regions. Following the toe graphaesthesia task, the brains of all three participants showed a conspicuous and qualitative increase in tracer uptake within the medial sagittal portions of the anterior one-third to one-half of the prefrontal regions. This pattern was the only consistent change for all three participants. The probability due to chance that this specific increase within the medial prefrontal regions would occur for all three participants (probability = $2/28 \times 2/28 \times 2/28$) was less than .001. The difference was clear and consistent during subsequent reconstructions of both data sets for each subject one year later. There was less obvious but perceptible focal activation noted over the left dorsolateral convexity of the left prefrontal region for two subjects and over the right prefrontal region for one subject following the toe stimulation.

Discussion

The results of this study suggest that the neurocognitive processes required for 10 min. of toe graphaesthesia, during which time the participant

must differentiate, identify, and articulate numbers drawn upon each of the toes, are associated with an increase of neuronal-glial activity within the anterior medial hemispheres. Specific activation in this portion of the cerebrum was predicted by the intercorrelational matrix between standardized scores for toe graphaesthesia and for tasks whose unique variance could be argued to be associated with this region of the brain (Persinger & Richards, 1995).

The possibility of confounding activation by simply stimulating the toes cannot be excluded from our results because toe gnosis was not one of the stimulus conditions. However, our patients who have sustained closed head injuries that were verified by either computerized tomography or magnetic resonance imaging have frequently displayed severely impaired toe graphaesthesia yet average toe gnosis. In addition, the shared variance between standardized scores for toe gnosis and for toe graphaesthesia was relatively small (less than 25%) within a population of 100 patients who had sustained closed head injuries (Persinger & Richards, 1995).

The activation within the medial parietal region during the baseline condition when the participants' eyes and ears were covered would be consistent with introspective activities. Recent metabolic studies have shown that reconstruction of (episodic) memory is associated with activation within the parietal region as well as within the anterior right lateral cortices (Ungerleider, 1995). Our observations of focal enhancement within the lateral prefrontal cortices would be consistent with the prevalence of thinking or introspection during the baseline conditions. Although vocalization during short-term memory activates the medial supplementary motor area (as well as the dorsolateral prefrontal cortices bilaterally) according to Fiez, Raife, Balota, Schwartz, Raichle, and Petersen (1996), the intensity and extent of the activation within the anterior medial prefrontal regions which we observed was quite rostral and extended well beyond the boundaries of the supplementary motor area.

A primary assumption of a complete neuropsychological assessment for patients who have sustained a closed head injury or traumatic brain injury is that the norm-referenced scores can be employed to infer the functional integrity of specific regions of the cerebrum (Persinger, 1995). By comparing the dozens of standardized scores for tasks that require general and specific cerebral functions, a mosaic of the patient's neurocognitive strengths and weaknesses can be discerned. The vectorial distribution of the hypofunction or damage (depending upon the severity of the impairment and the time since the injury) within the cerebrum can also be employed to test hypotheses concerning the directional propagation of counter-coup forces and to help devise strategies for the adaptation of the patient.

Traditional standardized neuropsychological assessments, from which

norm-referenced scores can be calculated, may not adequately sample the functions associated with most of the cerebral surface. For example, the tasks that compose the Halstead-Reitan Index (Reitan & Wolfson, 1985) primarily emphasize functions classically associated with the superior parietal, superior temporal, and dorsolateral prefrontal cortices. Although this index would be sensitive to gross or diffuse axonal injury that involved most of the cerebral volume or to very focal injuries within these specific cortices, one would not expect this index to be sensitive to even moderate dysfunction within other specific cortical regions, particularly the medial surfaces of the two hemispheres (Richards & Persinger, 1992; Persinger & Richards, 1995).

Our findings can be considered support for the construct validity of our measure. The unique variance associated with toe graphaesthesia involves relatively increased activity within the medial surfaces of the prefrontal cortices. To date, few clinical neuropsychologists employ an aggregate of norm-referenced procedures that would allow inferences about the integrity of this critical cortical region.

The unusual interhemispheric communications of major branches of the Anterior Cerebral Artery in a significant portion of the human population (about 25%) and the predilection of this region to shear or stress forces during nonfracturing closed-head injuries emphasize the importance of including valid measures for the integrity of the medial surfaces of the hemisphere. Without inclusion of psychometric inferences of the functional integrity of the anterior medial surfaces of the hemispheres, patients with specific anomalies within this region may be considered "not impaired" by traditional measures such as the Halstead-Reitan Index even though the disruption of function could seriously affect the patient's mood, sense of bonding within the family, and vocational adaptability.

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